PROSPECTIVE STUDY OF EFFECT OF CONVERTING ENZYME INHIBITORS ENALAPRIL VERSUS LISINOPRIL ON PROTEINURIA AND RENAL FUNCTION IN DIABETIC NEPHROPATHY.

THESIS

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T E A C H E R S

C E R T I F I C A T E

This is to certify that the work entitled "PROSPECTIVE STUDY OF EFFECT OF CONVERTING ENZYME INHIBITORS LISINOPRIL VERSUS ENALAPRIL ON PROTEINURIA AND RENAL FUNCTION IN DIABETIC NEPHROPATHY", which is being submitted as a thesis for M.D. (Medicine) Examination, 1995, Bundelkhand University, Jhansi, has been carried out by Dr. Nirmal Kumar in the Department of Medicine, M.L.B. Medical College, Jhansi.

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Dated : 20/2/95

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C O N T E N T S

I N T R O D U C T I O N

INTRODUCTION

Diabetes mellitus is a common serious metabolic disorder. Its true frequency varies from 1-2% in general population. Disease is characterised by metabolic abnormalities in form of hyperglycemia, hyperlipidemia and glycosuria and clinical presentation is in form of polyuria, polydipsia and polyphagia.

Common complications are retinopathy, diabetic nephropathy, atherosclerosis and ischemic heart disease and neuropathy.

Renal disease is the commonest complication and leading cause of death in diabetes. Diabetes affect the structure and function of kidney in many ways. Diabetic nephropathy is presented with variety of clinical syndromes like mild asymptomatic proteinuria, nephrotic syndrome, hypertension and progressive renal failure.

Diabetic nephropathy represents the single most important cause of renal failure in adults in the western world causing 25% of all new cases of uremia. The peak incidence of development of clinical disease occurs after about 16 years insulin dependent diabetes mellitus(IDDM). Overall, approximately 35-45% of patients with long standing insulin dependent diabetes mellitus will ultimately develop diabetic nephropathy defined as dip stick positive proteinuria, hypertension and falling GFR. (Christiansen and Andersen et al, 1985).

In insulin dependent diabetic patients incidence of nephropathy is 40-50% (Witzel et al, 1986). While less in non insulin dependent diabetes mellitus (NIDDM) one in four end stage renal disease patients turns out to be diabetic (Mogensen, 1984). The mortality in patients suffering from diabetic nephropathy is upto 100 times, that of age and sex matched background population and this is mainly due to enormous death from end stage renal disease (Borch Johansen et al, 1985).

Several lines of evidence indicate that renal hypertrophy and hyperfiltration are characteristics and early manifestation of human and experimental diabetes, which may contribute to later development of diabetic nephropathy. It also suggest that there is contribution of IGF-1 at very early stage to sequence of events that may lead to late diabetic nephropathy. Strict insulin treatment abolish both kidney IGF-1 accumulation and kidney growth.

Much has been learned in last decade regarding the pathology of the kidney in insulin dependent diabetes mellitus (IDDM) and non insulin dependent diabetes mellitus (NIDDM). The major pathologic changes of diabetes include thickening of all renal extracellular basement membranes and mesangial matrix and mesangial cell expansion. Although much less is known regarding renal pathology in NIDDM as compared to IDDM, most proteinuric patients with NIDDM have typical diabetic nephropathy while approximately 25% have

another forms of renal disease. Two renal lesions appear critical in diabetic nephropathy. Mesangial expansion out of proportion to the size of glomerulus is closely and inversely related to measures of peripheral capillary wall filtration surface, this expansion is also related to clinical features of proteinuria, hypertension and declining glomerular filtration rate(GFR). Arteriolar hyalinosis is related to global glomerulosclerosis and both are correlated with the clinical features of nephropathy. Renal extracellular basement membrane and matrix expansion appears to be secondary to increased production or decreased turnover, or both of normal structural constituents of the kidney. Microalbuminuria in the "Predictive range" is frequently accompanied by rising blood pressure and / or falling GFR and is associated with well established structural lesions. Thus microalbuminuria is a marker of quite advanced diabetic nephropathy.

The glomerular filtration of macromolecules is determined by intrinsic properties of glomerular capillary wall including size and charge selectivity and also by haemodynamic factors which govern GFR. Thus proteinuria can be altered by haemodynamic events such as changes in volume status or blood pressure independent of any changes in capillary wall structure.

During first decade of diabetes values for urine albumin excretion (AUE) rate usually remains normal averaging $<$10 mg/24 hours. There are however at least two

circumstances in which transient increase in UAE may be observed. First during episode of poor metabolic control and second during exercise mechanisms have not been fully characterised. Albumin excretion rate are rapidly reduced following improvement in metabolic control and cessation of exercise.

In patients with diabetes of several years duration, transient increase in UAE may result from the combination of altered glomerular haemodynamic function with early changes in glomerular capillary wall structure. In such patients exercise may serve as provocative test to reveal abnormalities in glomerular barrier function which are not apparent at rest.

Recent studies have shown that proteinuria in diabetic renal disease can be attributed to glomerular basement membrane thickening per se, it may well be caused by associated changes in basement membrane composition. It has been suggested that glycosylation of basement membrane constituents increases the permeability of basement membrane to macromolecules. In addition to this proteinuria may be related to changes in epithelial cell structure. It is not known whether these changes in epithelial cell structure represent a cause or consequence of increased glomerular permeability to macromolecules.

Microalbuminuria usually defined as having albumin excretion rates in range of 30-300 mg/24 hours and rates in excess of 500 mg/24 hours in turn reliably predict ultimate loss of kidney function in diabetic patients. The small

defect in glomerular barrier function which causes micro-albuminuria must therefore regarded as the first sign of pathological process which leads in exorable ~~in~~ renal failure.

Diabetic nephropathy is classified in five stages by Mogensen et al (1976).

Stage I : Early renal hypertrophy and hyperfunction.

Stage II : Renal lesion without clinical signs.

Stage III : Incipient diabetic nephropathy.

Stage IV : Clinical overt.

Stage V : End stage renal failure.

The observations that proteinuria precedes loss of renal function in diabetic patients has led to the assumption that maneuvers which reduces proteinuria will also retard the progression of diabetic renal disease. Morphometric studies suggest that the reduction of GFR in diabetic nephropathy is caused by progressive expansion of the glomerular mesangium. It is not certain that all maneuvers which reduce proteinuria will prevent reduction of GFR in diabetic patient.

Several therapeutic interventions, such as glycemic control, antihypertensive treatment and low to moderate protein diet have been shown to be effective in reducing microalbuminuria (Brouhard and Lagrone, 1990; Cievarella et al, 1987; Evanoff et al, 1987; Kupin et al, 1987; Rudberg et al, 1988 and Zeller et al, 1991).

The management of diabetic patients with advanced nephropathy is not easy because such patients tend to have the nephrotic syndrome and severe damage to many other organs consequently, it would be of great value to try and alleviate the massive proteinuria which is characteristic of this condition. In early stages of diabetic nephropathy several maneuvers and drugs have been tried to reduce the proteinuria and retardation of progression of nephropathy. Now-a-days ACE inhibitors are much in use specially Captopril, Enalapril for reduction of proteinuria and improvement of renal function in diabetic nephropathy cases.

ACE inhibitors are safe and effective antihypertensive agents that have unique beneficial intrarenal actions related to reduction of angiotensin II, intraglomerular pressures and glomerular permeability and possibly to normalization of mesangial function.

Recently Lisinopril which is being argued as a better ACE inhibitor as compared to Enalapril in the management of hypertension, has been utilized in diabetic nephropathy cases. One to the paucity of literature about the use of Lisinopril in diabetic nephropathy with or without hypertension, thus study has been designed to know the effect of Enalapril versus Lisinopril in cases of diabetic nephropathy.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

About 35 percent of patients with insulin dependent diabetes develop persistent proteinuria, a decline in glomerular filtration rate and increased arterial blood pressure, which collectively constitutes the clinical syndrome of diabetic nephropathy. The major pathologic changes of diabetes include thickening of all renal extracellular basement membranes and mesangial matrix and mesangial cell expansion. Although much less is known regarding renal pathology in NIDDM compared to IDDM. Most proteinuric patients with NIDDM have typical diabetic nephropathy while approximately 25 percent have another form of renal disease. It is commonly thought that nephropathy is more common in IDDM patients (Herman and Teutsch, 1985). Recent studies of diabetic Pima Indian suggest that cummulative risk of nephropathy in these NIDDM patients is at least as high as in IDDM patients. The high mortality is due to an excess of cardiovascular mortality and to end stage renal disease.

Several studies dealing with small number of patients have shown that effective antihypertensive treatment postpones renal insufficiency in insulin dependent diabetes with nephropathy.

ACE INHIBITORS

Renin is an enzyme produced by kidney in response to adrenergic activity and to sodium depletion.

Renin converts a circulating globulin (angiotensinogen) into biological inert angiotensin I which is then changed by angiotensin converting enzyme (ACE) into the highly potent vasoconstrictor angiotensin II. Angiotensin II also stimulated production of aldosterone (sodium retaining hormone by the adrenal cortex). It is evident that angiotensin II can have an important effect on blood pressure.

ENALAPRIL

This is nonsulfhydryl second generation ACE inhibitor well absorbed after oral doses 5-20 mg as single dose. Its peak concentration reaches within an hour. De-esterification occurs in liver with peak concentration of its active metabolic enalaprilate within 4 hours. It decreases the blood pressure by inhibiting the generation of angiotensin II and retarding the degradation of bradykinins (vasodilators) and decreases the proteinuria by decreasing net filtration pressure in glomerulus by dilating both the afferent and efferent arterioles of glomerulus (Efferent arteriolar dilatation much more than afferent one).

LISINOPRIL

Lisinopril a long acting ACE inhibitor is a lysine derivative of enalaprilate, athe active angiotensin converting enzyme inhibitor metabolite of enalapril. Lisinopril decreases plasma concentration of angiotensin II and aldosterone.

About 20-25 percent of an oral dose of lisinopril becomes bioavailable in man and peak serum concentration of Lisinopril is reached in about 6 hours. Absorption is unaffected by food. Lisinopril is active by itself and does not require to undergo activation in the liver. Absorbed drug is primarily excreted unchanged in urine.

The initial starting dose of Lisinopril is 5-10 mg/dl dosage should be adjusted according to blood pressure response. Dosage can be increased upto maximum 80 mg once daily. In hypertensive patients with severe renal impairment or with renal artery stenosis, dosage should be reduced.

Side effects of ACE inhibitors are hypotension, cough, headache, dizziness, angioneurotic oedema, urticaria, Rashes, leucopenia, loss of appetite, diarrhoea and may cause renal failure.

Vibreti and Hill et al (1982) studied that the overnight urinary albumin excretion rates (AER) in 87 patients with insulin dependent diabetes mellitus has measured in 1966-67. Fourteen year later information was obtained on 63 of original cohort, these alive were restudied and for those who had died relevant clinical information and cause of death were recorded. The development of clinical diabetic nephropathy (Albustix-positive proteinuria) was related to the 1966-67 AER values. Clinical proteinuria developed in only 2 of 55 patients with AER below 30 ug/min but in 7 of 8 with AER between 30 and 140 ug/min. The risk of clinical diabetic nephropathy in the later group was twenty four times higher than in the former. 9.1% of

patients with AER below 30 ug/min had died, compared with 37.5% with higher AER. The two groups did not differ significantly in age, sex, composition and initial blood pressure. Thus elevated levels of microalbuminuria strongly predict the development of clinical diabetic nephropathy. These levels of AER are potentially reversible and their detection and treatment may prevent diabetic renal disease.

Among therapies examined to date, antihypertensive agents have proven most effective in reducing proteinuria in patients with diabetic renal disease. Moreover, antihypertensive agents have the same effect on glomerular barrier function over all, studies to date suggested that albumin excretion rates are comparably reduced the regimens including converting enzyme inhibitors and beta adrenergic blockers, while variable effects on albumin excretion rates have been observed with calcium channel blockers.

The mechanism by which antihypertensive agents improve glomerular barrier function in diabetic renal disease have not been fully elucidated. It has frequently been suggested that antihypertensive agent improve glomerular barrier function by lowering glomerular transcapillary hydraulic pressure $\triangle P$. A recent modification of this "haemodynamic hypothesis" suggested that antihypertensive agents improve glomerular barrier function by reducing glomerular capillary wall tension, which is considered to be the product of $\triangle P$, and glomerular capi-

llary radius, studies in which converting enzyme inhibitor treatment was initiated at the outset of experimental diabetes are often cited in support of this hypothesis.

These studies have shown that continuous converting enzyme inhibitor treatment reduces $\triangle$ P and largely prevents development of albuminuria in rats (Zatz et al, 1986).

A recent dextran clearance study suggest alternatively that converting enzyme inhibitor therapy may have direct effect on glomerular capillary wall pore structure (Morelli E, Loon, Myer TW, Peter SW, Meyer, BD). Converting enzyme inhibitor treatment decreases fractional clearance values not only for large dextran molecules with radii 50-60 A^{o} but also for dextran molecules with radii of 30-50 A^{o}. This finding suggests that converting enzyme inhibitor therapy alters the structure of capillary wall so as to shift the entire pore sized distribution towards lower values.

Nyberg et al suggested that hyperglycemia is a risk factor for the progression of clinical diabetic nephropathy in insulin dependent diabetic patients with impired renal function(glomerular filtration rate $<$50 ml/min).

Zatz et al (1986) reported significant beneficial effects of Enalapril treatment in experimental diabetic nephropathy. Twelve months of observation in diabetic controls and Enalapril treated diabetic rats showed that

proteinuria was prevented after ACE inhibition. Micropuncture results obtained 4-6 weeks after onset of diabetes confirmed reduction of glomerular transcapillary pressure difference after ACE inhibitor without changes of GFR or glomerular plasma flow. They concluded that prevention of glomerular capillary hypertension in rats with diabetes reduces glomerular structural damage.

Bjorck et al (1986), Hommel et al (1986) and Taguma et al (1986) suggested that ACE inhibitor may arrest the progressive rise in the albuminuria regardless of the absence or presence of systemic hypertension in diabetic patients with nephropathy.

Parving et al (1987) showed that blood pressure is very important for renal function in diabetic nephropathy. Treatment of hypertension has been repeatedly documented as beneficial in reducing the rate of deterioration of renal functions when nephropathy is present.

Extensive experimental studies as well as some limited clinical observations suggest that angiotensin II plays an important intrarenal role in genesis or aggrevation of excessive glomerular protein filtration.

TABLE : Angiotensin II and glomerular haemodynamics.

	Angiotensin II	ACE inhibitor
Afferent arteriolar resistance	↕	↓
Efferent arteriolar resistance	↑	↓
Glomerular capillary pressure	↑	↓
Glomerular capillary permeability	↑	↓
Filtration surface area	↓	↑

Table summarises the effects of angiotensin II and ACE inhibitor on glomerular haemodynamics. Blockade of angiotensin II synthesis with ACE inhibitors have been shown to reduce protein excretion in experimental models of subtotal nephrectomy and diabetic and membranous nephropathy. Clinical improvement has been noted in patients with diabetic nephropathy and with diverse renal parenchymal disease that result in proteinuria greater than 1 gm/24 hours. The long term consequence of ACE inhibition in reducing blood pressure and proteinuria should be salutary because of the effect on pressure and also because a reduction of filtered load of protein results in the reduction in mesangial processing of protein macromolecules.

Treatment with ACE inhibitor is theoretically considered to cause a preferential dilatation of efferent glomerular arterioles and ultimately a decrease in intra-glomerular capillary pressure and urinary albumin excretion (Bauer and Ream, 1986, Williams, 1988).

Many studies using ACE inhibitors such as captopril, Enalapril, Lisinopril, perindopril have indicated an antiproteinuric potential in diabetic patients with nephropathy (Barkis, 1990, Bejer et al, 1987, Christiansen et al, 1988, Doyle et al, 1988, Pelici et al, 1988, Hommel et al, 1986, Marre et al, 1987, Marre et al, 1988, Parving et al, 1988, Passa et al, 1987 and Taguma et al, 1985).

According to Gavras (1988) Lisinopril retards diabetic nephropathy. In fact the improved renal perfusion tends to ameliorate impaired renal function and alteration of intrarenal haemodynamics rends to lessen proteinuria and retard diabetic nephropathy.

A few recent short term controlled trials compared on ACE inhibitor (Captopril or Lisinopril) with dihydropyridine calcium antagonist, Nifedipine and suggested that ACE inhibitors may have an advantageous antiproteinuric effect over Nifedipine (Berg et al, 1989, Insera et al, 1988, Mimran et al, 1988 and Ramanelli et al, 1989).

Such an antialbuminuric effect has also been observed in normotensive diabetic patients treated with Enalapril (Pedersen et al, 1988, Rudberg et al, 1990).

Heeg and de Jong (1989) studied the effect of Lisinopril in 12 patients with overt proteinuria (range 3.2 - 10.5 g/day) with normal or elevated blood pressure (diastolic BP - 64 - 105 mm Hg) and with varying GFR (34 - 127 ml/min). Sodium intake was set at 50 m mol/day and all medication was withdrawn for at least 2 weeks. The study involved four, 2 month periods. 1. control, 2. alpha methyldopa MD to test the effect of BP lowering. 3. Lisinopril 5 mg/day and 4. Lisinopril 10 mg/day. Proteinuria did not change from control to methyldopa (6.0 ± 2.3 to 6.1 ± 2.1 g/day) and fell by $26 \pm 20\%$ ($p < 0.002$) on 5 mg Lisinopril and by $50 \pm 17\%$ ($p < 0.001$) on 10 mg Lisinopril to 3.1 ± 1.4 g/day. Blood pressure decreased as compared to control by

11±7%, 13±7% and 16±6% respectively. The fall in proteinuria was similar in patients with MAP 7 or ⟨100 mm Hg and in patients with GFR 7 or ⟨75 ml/min. Moreover, no correlation existed between fall in proteinuria and initial blood pressure, GFR or proteinuria interestingly when the patients switched during Lisinopril from low to high sodium intake (200 ml/day proteinuria rose to control value (5.9±3.0 g/day). The concluded that Lisinopril reduces overt proteinuria irrespective of initial blood pressure, GFR and proteinuria. This effect is dose related and appears dependent on adequate sodium restriction.

Gorden (1990) showed that hypertension significantly add the risk of renal damage in diabetic patients and had a higher level of plasma angiotensin II during follow up period.

According to retrospective study conducted by Johannes FE et al (1990) ACE inhibitors are more effective than other anti-hypertensive agents in reducing the progression of renal failure.

According to Ronald, Rodel and Mulcahy (1990) Enalapril showed to have a beneficial effect on renal function and proteinuria in patients with renal failure.

Ueda, Aoi, Yamachika, Shikaya (1990) showed that Enalapril therapy significantly produces a fall in blood pressure, increase the blood flow, produces a change in GFR and might improve the glucose homeostasis.

According to Ferder Inserra Oaccordi. Smith (1990) Enalapril therapy may improve the prognosis for glomerulopathies over time by maintaining glomerular filtration rate and decreasing proteinuria.

Bjorck et al (1990) compared the renal effects of Enalapril and metaprolol in 40 IDDM patients with a reduced renal function and found that on 8 weeks treatment with Enalapril was more effective in reducing proteinuria than with metaprolol.

In the study by Mathiesen et al (1991) patients with albumin excretion of 70-200 ug/min seemed to benefit most from treatment with angiotensin converting enzyme inhibitor.

Angiotensin converting enzyme inhibitors seem to work at several stages in the development of diabetic renal disease - normoalbuminuria, microalbuminuria and overt nephropathy and to have several different actions. These include effects on systemic hypertension (Mogensen et al, 1988), the glomerular membrane (Morelli and Loon et al,1990) and possibly the growth characteristics of glomerular tissues which may be relevant to pathogenesis of renal disease (Ichikawa et al, 1991 and Flyvbjerg et al, 1991).

Apperloo, Zeeuk et al (1992) found that Lisinopril in addition to reduction in blood pressure, clinically important effect of the drug appeared to be its antiproteinuric effect. They found approximately 60% decrease in

urinary protein excretion. They suggested that this anti-proteinuric effect is not only the result of hypotensive effect of drug, but probably also is due to a fall in intra-glomerular capillary pressure, such a fall in intraglome-rular capillary pressure can also be important contributing factor in the retardation of progressive impaired renal function. Indeed it has been suggested that ACE inhibitors have therapeutic potential to retard a decline in renal function.

Bauer, Reams and Hewett (1992) reported the results of a randomized double blind clinical trial designated to compare the longitudinal (18 months) effects of an ACE inhibitor (Enalapril) and a placebo an urinary protein excretion and the rate of progression of renal disease in 33 patients with clinical diabetic nephropathy. Systemic blood pressure was controlled with the use of conventional antihypertensive drugs. Their results confirmed that ACE inhibitor therapy is antiproteinuric in dependent of systemic blood pressure control. However, the rates of progression of renal disease were not significantly different between two treatment groups. Further more, a prolonged decrease in 24 hour urinary protein excretion did not predict attenuation of progression of established disease.

Ciavarella and Mustacchio et al (1992) investi-gated the effect of low doses of angiotensin converting

enzyme inhibitor Enalapril (5-10 mg/day) on renal haemodynamics and albuminuria in normotensive and hypertensive type I (insulin dependent) diabetic patients with incipient or overt nephropathy. After 3 months run in period they observed that administration of Enalapril resulted in both groups of patients in a significant fall in mean arterial pressure, albumin excretion rate, glomerular filtration rate, filtration fraction, and renal vascular resistance. Their results suggest that low doses of Enalapril is effective in influencing renal haemodynamics and reducing urinary albumin excretion in both normotensive and hypertensive type I diabetic patients with incipient or overt nephropathy. The lowering effect of ACE inhibitor on albuminuria seems to be independent of the action on systemic blood pressure and renal haemodynamic changes.

Slataper et al (1993) compared the effects of different antihypertensive agents on progression of diabetic renal disease and they concluded that given a similar level of arterial pressure control both Lisinopril and Diltiazem slow progression of diabetic renal disease and reduced albuminuria to a greater extent than does the combination of a loop diuretic and beta adrenoreceptor antagonist. These drugs were also better tolerated and produced no adverse metabolic effects.

Ravid M, Savin, H et al (1993) concluded that in normotensive patients with diabetes mellitus type II the institution of angiotensin converting enzyme inhibition during early stages of diabetic nephropathy results in long term stabilization of plasma creatinine levels and of the degree of urinary loss of albumin. These effects are probably independent of the antihypertensive action of these agents.

Melchior, Bindlish and Jaber (1993) concluded that ACE inhibitors delay the onset and slow the progression of diabetic nephropathy in people with diabetes independent of blood pressure effects. They also show the progression of diabetic nephropathy in people with diabetes who have poorly controlled hyperglycemia. The proper dose and time to prevent the appearance of diabetic nephropathy is not known. It is also not known how long the beneficial effect of ACE inhibitor therapy persists.

O'Donnell et al (1993) reported the result of placebo controlled trial of Lisinopril in normotensive diabetic patients with incipient nephropathy. There were 27 patients with type I and type II diabetes with an albumin excretion rate of between 20 ug/min and 200 ug/min, respectively. Intervention treatment with placebo or low dose Lisinopril was for 48 weeks (12 Lisinopril 15 placebo) After 48 weeks treatment seven Lisinopril treated patients were normoalbuminuric and five were microproteinuric. Three placebo treated patients were normoalbuminuric, nine were [illegible] and three were macroproteinuric.

Barkis , Slataper and Vicknair et al (1994) studied the effect of Lisinopril on renal size and microalbuminuria in normotensive IDDM patients. Evaluation at 18 months demonstrated that there was a marked reduction in renal size (16.9±1.1 baseline versus 12.8±0.9 cm, 18 months; <0.05) and microalbuminuria (92±11 ug/min, baseline versus 23±32 ug/min, 18 months; $p<0.05$).

TABLE : Result of 10 published studies of the effects of ACE inhibitors in patients with diabetes mellitus.

Authors	No.of cases	Type of Diab.	Time (month)	Drug	B.P. mm Hg	Urinary protein	Glucose tolerance	Serum creatinine	GFR	RPF	FF
Short term studies											
Taguma et al	10	I	3	C	-5/-3	-	NC	NC	NR	NR	NR
Hommel et al	16	I	3	C	-12/-8	-	NC	-	-	NR	NR
D'Angelo et al	10	I	3	C	-19.4	NC	NC	-	NC	NC	NC
	10	II	3	C	-23.7	NC	NC	-	NC	NC	NC
Mathew et al	13	II	1.5	C	-19/-14	NR	NC	NR	NR	NR	NR
Dominguez et al	8	II	3	C	-43/-12	NR	Improved	NC	NR	NR	NR
Winocour et al	8	I	1.5	C	-	NC	NR	-	NC	NC	NC
Sullivan et al	10	I+II	3	C	-14/-8	NR	NC	NC	NR	NR	NR
Long term studies											
Bjorck et al	14	I	12	C	-5	NC	NC	NC	NC	+	-
Passa et al	11	I	12	C	-32/-19	NC	NC	NR	NC	NR	NR
Marre et al	10	I+II	6	E	-13/-10	-	NC	NC	+	+	NC

NC = No change, NR = Not reported, + = Increased, - = Decreased, C = Captopril, E = Enalapril, RPF = Renal plasma flow, FF = Filtration fraction, Diab. = Diabetes.

AIMS AND OBJECTIVES OF THE STUDY

This study has been designed to find out the effect of Enalapril versus Lisinopril in diabetic nephropathy with or without hypertension on :

a. Albuminuria.

b. Renal function.

MATERIAL AND METHODS

MATERIAL AND METHODS

The study was conducted on the patients of diabetic nephropathy, attending the diabetic and nephrology Clinics of out patient department and admitted in M.L.B. Medical College, Hospital, Jhansi.

The history was taken from all the patients of diabetes to know the duration of symptoms, year of diagnosis, type of diabetes, familial relation and complications of diseases.

General as well as systemic examinations were recorded to know the general condition, pulse rate, blood pressure, temperature, pallor, icterus, cyanosis, clubbing, oedema, hydration and lymphadenopathy. Systemic examination was done to find out the changes in all systems due to diabetes. The patients having diseases other than diabetes were excluded from the study.

Dipstick test and fundoscopy were done to find out the proteinuria and retinopathy. After confirmation of the diabetic nephropathy, the patients were investigated for 24 hour proteinuria, blood urea, and serum creatinine.

The blood pressure was recorded before starting drugs. The Enalapril and Lisinopril were given to the alternate patient respectively. The doses of drugs were adjusted according to the blood pressure response. Hypoglycemic drugs were given according to blood sugar levels.

After 8 weeks course of converting enzyme inhibitors, patients were further investigated for 24 hour urine albumin excretion, blood urea and serum creatinine. At last, the results were compiled to know the efficacy of drugs in relation to reduction in albuminuria and improvement in renal functions of individual drugs as well as statistical analysis was done to find out the difference in efficacy.

URINE ALBUMIN

A quantitative estimation of albumin was done by turbidity method as described by Wooten (1964).

Reagents

Sulphosalicylic acid (3%), 3.0 gm of sulphosalicylic acid was dissolved in 100 ml distilled water. Albumin standard solution (100%) in 100 ml distilled water, 100mg crystalline bovine albumin was dissolved and kept in refrigerator.

Procedure

Twenty four hours urine was collected in bottle which was marked in milli litres so the 24 hour urinary volume was measured and noted. Toluine was used as preservative. Required amount was then taken from it and centrifuged.

Test :	1. Urine	1.0 ml
	2. Sulphosalicylic acid solution	4.0 ml

Standard :	1. Albumin standard solution	1.0 ml
	2. Sulphosalicylic acid solution	4.0 ml
Blank :	1. Urine	1.0 ml
	2. Water	4.0 ml

The tubes were kept for 30 minutes and then the absorbance was measured with blue filter (450 nm) against reagent blank.

Calculations

$$\text{Urinary albumin (mg/dl)} = \frac{\text{Reading of test}}{\text{Reading of standard}} \times 100$$

BLOOD UREA (Diacetyl Monoxime method)

Reagents

1. Diacetyle mono-axime reagent : 2.0 gm pure diacetyl mono-axime was dissolved in 60 ml double distilled water and 2 ml glacial acetic acid was mixed and made it 100 ml with double distilled water.
2. Acid mixture : 150 ml of 85% phosphoric acid was added to 140 ml of double distilled water. Mixed well, 50 ml of concentrated sulphuric acid was added slowly.
3. Trichloroacetic acid solution : 10 gm TCA dissolved in 100 ml of double distilled water.
4. Urea stock standard : 250 mg of pure urea crystals dissolved in 100 ml double distilled water.
5. Working urea standard : 1 ml of stock solution was diluted in 100 ml of double distilled water. This solution contains 0.25 mg/urea/ml.

Method

0.1 ml blood sample was added in a tube containing 1.9 ml double distilled water. It was mixed thoroughly and 2.0 ml 10% TCA solution was added and centrifuged the content at 3000 rpm for 5 to 10 minutes. 2 ml supernatant was taken in a test tube and it was marked as 'T' representing the test blood sample filtrates.

Standard

1.0 ml working urea solution was added in 1.0 ml of double distilled water. It was marked as 'S' representing standard solution.

Blank

2.0 ml double distilled water was taken and it was marked as 'B' representing the blank system.

Thereafter, 0.4 ml diacetyl mono-axime reagent and 1.6 ml acid mixture were added in each system. Mixed well and incubate for 30 minutes in boiling water bath. After that test tubes were taken out and measured the samples at 480 nm by setting the spectrometer zero with the blank system.

Calculation

$$\text{Blood urea (mg/dl)} = \frac{\text{Reading of unknown}}{\text{Reading of standard}} \times 100$$

SERUM CREATININE (Alkaline picrate method)

Reagents

1. Picric acid solution : Picric acid solution was prepared in double distilled water. This solution is called to be saturated when crystal was of picric acid settled down at the bottom and did not dissolve even after thorough mixing.
2. Sodium hydroxide 0.75 N solution : It was prepared by dissolving 30 gm of sodium hydroxide in 1 litre of double distilled water.
3. Sodium Tungustate (57 w/v) : It was prepared by dissolving 5.0 gm pure sodium tungustate in 100 ml double distilled water.
4. Sulphuric acid (2/3N) : It was prepared by mixing 10 ml concentrated sulphuric acid to the 900 ml double distilled water and made upto the 1 litre with water.
5. Stock creatinine standard : 20 mg pure creatinine was dissolved in 100 ml double distilled water. It was 20 mg% creatinine solution.
6. Working creatinine standard : 10 ml of creatinine stock solution was diluted with 10 ml double distilled water. It was 2 mg% creatinine solution.

Method

Sets of 3 test tubes were taken and marked as 'T' for test, 'S' for standard and 'B' for blank .

Solutions were taken as follows :

In 'T' test tube : 10 ml serum and 1.0 ml D.D.W.

In 'S' test tube : 2 ml working creatinine standard solution.

In 'B' test tube : 20 ml double distilled water.

After that 1 ml 5% sodium tungustate solution and 1 ml 2/3 N sulphuric acid were mixed and centrifuged for 5 to 10 minutes at 3000 rpm.

In another set of the test tubes marked with 'T', 'S' and 'B' the 2 ml supernatant was taken from the above respective systems. Now 0.5 ml picric acid solution and 0.5 ml 0.75 N sodium hydroxide solution were used respectively in each system. It was incubated at room temperature for 20 minutes and readings were taken from the test and standard samples at 520 nm by setting the spectrometer zero with the blank.

Calculation

$$\text{Serum creatinine (mg/dl)} = \frac{\text{Reading of unknown}}{\text{Reading of standard}} \times 4$$

O B S E R V A T I O N S

OBSERVATIONS

A total of 56 patients were included in the present study, who were attending diabetic clinic regularly in M.L.B. Medical College, Hospital, Jhansi (UP). Out of 56 patients 25 patients were put in Enalapril group while remaining 31 patients in Lisinopril group. Out of 25 patients of Enalapril, 13 were on insulin therapy and rest 12 were on oral hypoglycemic agents. Out of 31 patients of Lisinopril group, 15 were on insulin therapy while rest 16 were on oral hypoglycemic agents. Blood pressure as well as glycemic control was satisfactory in follow up period.

TABLE I : Distribution of cases of Enalapril group according to their age and sex.

Age group (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
21 - 30	-	-	-	-	-	-
31 - 40	4	23.54	2	25.00	6	24.00
41 - 50	6	35.29	4	50.00	10	40.00
51 - 60	6	35.29	1	12.50	7	28.00
61 - 70	1	5.88	1	12.50	2	8.00
TOTAL	17	100.00	8	100.00	25	100.00

Table I shows that there were 25 patients in this group. Out of which 17 were males and 8 females. The maximum (40%) cases belonged to 41-50 years of age group. Male patients were maximum in age group of 41-50 years (35.29%) where females patients were maximum (50%) in the age group of 41-50 years.

TABLE II : Distribution of cases of Lisinopril group according to their age and sex.

Age group (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
21 - 30	2	10.00	-	-	2	6.45
31 - 40	-	-	2	18.20	2	6.45
41 - 50	5	25.00	2	18.20	7	22.52
51 - 60	6	30.00	4	36.40	10	32.29
61 - 70	7	35.00	3	27.20	10	32.29
TOTAL	20	100.00	11	100.00	31	100.00

Table II shows age and sex distribution of cases of Lisinopril group. There were 31 patients in this group. Out of which 20 were males and 11 females. The maximum (64.58%) cases belonged to 50-70 years of age group. Male patients were maximum in the age group of 61-70 years (35%) whereas females were maximum (36.4%) in the age group of 51-60 years of age group.

TABLE III : Distribution of cases of Enalapril group according to duration of diabetes mellitus.

Duration of DM (years)	No.of cases	Percentage
1 - 5	3	12.00
6 - 10	15	60.00
11 - 15	6	24.00
16 - 30	1	4.00
TOTAL	25	100.00

Table III shows the distribution of cases of Enalapril group according to their duration of diabetes mellitus. The maximum (60%) cases belonged to 6-10 years of duration of diabetes mellitus whereas minimum (4%) cases were in the range of 16-30 years of duration.

TABLE IV : Distribution of cases of Lisinopril group according to duration of diabetes mellitus.

Duration of DM (years)	No.of cases	Percentage
1 - 5	5	16.13
6 - 10	9	29.03
11 - 15	12	38.71
16 - 30	5	16.13
TOTAL	31	100.00

Table IV shows the distribution of cases of Lisinopril group according to their duration of diabetes mellitus. The maximum (38.71%) cases belonged to 11-15 years duration.

TABLE V : Distribution of cases of Enalapril group according to their sex and mode of treatment.

Mode of treatment	Male		Female		Total	
	No.	%	No.	%	No.	%
Oral hypoglycemic group	11	64.71	1	12.50	12	48.00
Insulin group	6	35.29	7	87.50	13	52.00
TOTAL	17	100.00	8	100.00	25	100.00

Table V shows that of 12 (48%) patients belonged to oral hypoglycemic group (11 males and 2 females) and 13 (52%) belonged to insulin group (5 males and 7 females.

TABLE VI ; Distribution of cases of Lisinopril group according to their sex and mode of treatment.

Mode of treatment	Male		Female		Total	
	No.	%	No.	%	No.	%
Oral hypo-glycemic	10	50.00	6	54.40	16	51.60
Insulin group	10	50.00	5	45.60	15	48.40
TOTAL	20	100.00	11	100.00	31	100.00

Table VI shows the mode of treatment and sex incidence, in Lisinopril group of patients. There were 31 patients in this group. Out of which 20 were males and 11 females. Out of 20 males, 50% were on oral hypoglycemic agents, and rest 50% were on insulin therapy. While 54.4% females were on oral hypoglycemic agent and 45.6% in insulin therapy. The maximum number of cases (51.60%) were on oral hypoglycemic agents.

TABLE VII : Showing the effect of Enalapril on blood pressure in cases of oral hypoglycemic agents

Case No.	Blood pressure(mm Hg)			
	0 month		2 months	
	Systolic	Diastolic	Systolic	Diastolic
1	116	80	104	72
2	140	82	146	80
3	158	92	160	94
4	152	84	150	80
5	104	72	100	70
6	146	84	140	80
7	144	92	140	90
8	146	96	150	100
9	130	88	110	80
10	108	86	110	80
11	150	92	140	86
12	138	72	134	82
Mean± S.D.	136.00 ±17.75	85.00 ±7.70	132.00 ±20.45	82.83 ±8.55

0 - 2 months : Systolic BP $p < 0.05$

Diastolic BP $p < 0.05$

Table VII shows the effect of Enalapril on systolic and diastolic blood pressure in patients on oral hypoglycemic agents after 2 months of therapy. The initial systolic BP was 136±17.75 mm Hg which came down to 132±20.45 mm Hg after 2 months therapy. The difference was statistically significant ($p < 0.05$). Similarly the diastolic BP fell down from initial 85±7.70 mm Hg to 82.83±8.55 mm Hg after 2 months therapy which was also significant ($p < 0.05$).

TABLE VIII : Showing the effect of Lisinopril on blood pressure in cases of oral hypoglycemic group.

Case No.	Blood pressure (mm Hg)			
	Systolic 0 month		2 months	
	Systolic	Diastolic	Systolic	Diastolic
1	126	76	124	74
2	120	70	110	74
3	110	80	100	80
4	190	120	160	100
5	126	74	130	78
6	140	90	124	86
7	160	90	150	90
8	170	120	160	100
10	180	94	170	92
11	194	90	276	88
12	138	72	140	80
13	200	100	170	90
14	132	76	112	70
15	138	90	150	88
16	140	80	130	84
Mean ±S.D.	152.13 ±27.99	88.88 ±15.42	140.38 ±23.22	85.88 ±8.88

o - 2 months : Systolic BP $p < 0.01$
Diastolic BP $p < 0.01$

Table VIII shows the effect of Lisinopril on systolic and diastolic blood pressure in patients on oral hypoglycemic agents after 2 months therapy. The initial systolic BP was 152.13±27.99 mm Hg which came down to 140.38±23.22 mm Hg after 2 months therapy with Lisinopril

and their difference was statistically significant($p < 0.01$) whereas the diastolic blood pressure fell down from initial 88.88 ± 15.42 to 85.38 ± 8.88 mm Hg after 2 months which was also statistically significant ($p < 0.05$).

TABLE IX : Statistical analysis of table VII and VIII.

Blood pressure	p values	
	0 month	2 months
Systolic	< 0.05	< 0.05
Diastolic	< 0.05	< 0.05

Table IX shows the comparison of previous two tables at 0 and 2 months therapy. According to this table there was statistically significant difference between the effect of Enalapril and Lisinopril in systolic and diastolic blood pressure at 0 and 2 months therapy.

Table X shows the effect of Enalapril on both types of blood pressure in patients on insulin. The initial systolic BP was 134.46 ± 19.01 mm Hg which came down to 131.38 ± 15.95 mm Hg after 2 months therapy and the difference was statistically significant ($p < 0.05$). Likewise diastolic BP fell down from initial 82 ± 10.65 mm Hg to 80.46 ± 9.32 mm Hg after 2 months therapy and the difference was also statistically significant ($p < 0.05$).

TABLE X : Showing the effect of Enalapril in blood pressure in patients of insulin therapy.

Case No.	Blood pressure (mm Hg)			
	0 month		2 months	
	Systolic	Diastolic	Systolic	Diastolic
1	116	80	114	76
2	140	74	130	70
3	170	100	160	98
4	136	92	130	88
5	140	80	138	78
6	100	60	102	64
7	140	92	146	90
8	162	86	150	84
9	140	78	136	76
10	130	82	132	80
11	110	68	112	70
12	128	86	124	84
13	136	88	134	86
Mean ±S.D.	134.46 ±19.01	82.00 ±10.65	131.38 ±15.95	80.46 ±9.32

0 - 2 months : Systolic BP $p < 0.05$
diastolic BP $p < 0.05$

Table XI shows the effect of Lisinopril on systolic and diastolic BP in patients on insulin. The initial systolic BP was 147.47±20.97 mm Hg which came down to 139.73±19.34 mm Hg and the difference was significant ($p < 0.05$) whereas diastolic BP fell down from initial 85.07±10.74 to 82.27±8.65 mm Hg after 2 months therapy which was also significant statistically ($p < 0.05$).

TABLE XI : Showing the effect of Lisinopril on blood pressure in patients on insulin.

Case No.	Blood pressure (mm Hg)			
	0 month		2 months	
	Systolic	Diastolic	Systolic	Diastolic
1	140	80	130	76
2	130	90	150	90
3	120	70	110	70
4	160	90	110	80
5	150	90	120	80
6	142	86	130	82
7	190	106	170	96
8	128	80	154	80
9	140	90	134	84
10	190	90	168	96
11	130	80	128	82
12	160	92	150	84
13	150	92	140	90
14	130	60	138	64
15	152	80	164	80
Mean ±S.D.	147.47 ±20.97	85.07 ±10.74	139.73 ±19.34	82.27 ± 8.65

o - 2 months : Systolic BP $p < 0.05$
Diastolic BP $p < 0.01$

TABLE XII : Showing the statistical comparison of tables X and XI.

Blood pressure	p value	
	0 month	2 months
Systolic	< 0.05	> 0.05
Diastolic	> 0.05	> 0.05

Table XII shows the comparison of previous tables X and XI at 0 and 2 months therapy according to the table initial values of systolic blood pressure was statistically significant and all other values were statistically insignificant ($p > 0.05$).

TABLE XIII : Showing the effect of Enalapril on 24 hours urinary albumin excretion in patients on oral hypoglycemic agents.

Case No.	Urine albumin (mg/24 hours)	
	0 month	2 months
1	40	60
2	48	30
3	400	40
4	100	40
5	80	40
6	60	20
7	60	20
8	120	100
9	920	800
10	120	60
11	240	640
12	240	320
Mean±S.D.	202.33±249.84	180.83±266.80

0 - 2 months : $p > 0.05$

Table XIII shows the effect of Enalapril on urinary albumin excretion in patients on oral hypoglycemic ahents. At the start of treatment the mean excretion was 202.33±249.84 which was decreased to 180.83±266.80 mg/ 24 hours after 2 months therapy of Enalapril. The difference was not significant statistically (p >0.05).

TABLE XIV : Showing the effect of Lisinopril on 24 hours urinary albumin excretion in patients on oral hypoglycemic agents.

Case No.	Urine albumin (mg/24 hours)	
	0 month	2 months
1	140	60
2	220	520
3	900	300
4	220	20
5	80	20
6	60	20
7	460	800
8	880	600
9	240	880
10	60	200
11	80	20
12	700	400
13	740	200
14	320	300
15	180	60
16	160	60
Mean±S.D.	340.00±298.70	278.75±286.25

0 - 2 months : p >0.05

Table XIV shows the effect of Lisinopril on 24 hours urinary albumin excretion in patients on oral hypoglycemic agents. Initial mean urinary albumin excretion was 340.0±298.70 mg/24 hours. After 2 months therapy of Lisinopril it was only 278.75±286.25 mg/24 houes. The difference between 0 and 2 months values was not statistically significant (p >0.05).

TABLE XV : Showing the comparison of tables XIII and XIV.

Treatment group (oral hypoglycemic agents)	Values of albuminuria (Mean±S.D.)	
	0 month	2 months
Enalapril	203.33±294.84	180.83±266.80
Lisinopril	340.00±298.70	278.75±286.82
p values	>0.05	>0.05

Table XV shows the comparison of 0 and 2 months therapies of table XIII and XIV. At 0 month the 24 hours urinary protein excretion was higher in patients of Lisinopril group but the difference was statistically insignificant (p >0.05). After 2 months therapy both the values were not statistically significant (p >0.05).

TABLE XVI : Showing the effect of Enalapril on 24 hours urinary albumin excretion in patients on insulin.

Sl. No.	Urine albumin (mg/24 hours)	
	0 month	2 months
1	80	30
2	360	320
3	120	360
4	100	30
5	60	20
6	800	640
7	40	120
8	360	280
9	80	64
10	320	240
11	80	48
12	60	40
13	720	620
Mean±S.D.	245.23±256.79	216.30±219.53

0 - 2 months : $p > 0.05$

Table XVI shows the effect of Enalapril on 24 hours urinary albumin excretion in patients on insulin. Initially 24 hours protein excretion was 245.23±256.79 mg/24 hours which came down to 216.30± 219.53 mg/24 hours but the difference was statistically insignificant ($p > 0.05$).

TABLE XVII : Showing the effect of Lisinopril on 24 hours urinary albumin excretion in patients on insulin.

Case No.	Urine albumin (mg/24 hours) 0 month	2 months
1	580	240
2	88	40
3	240	160
4	80	20
5	880	1000
6	320	120
7	720	800
8	160	80
9	370	60
10	720	320
11	60	180
12	140	20
13	60	20
14	800	60
15	60	180
Mean±.S.D.	351.87±304.43	220.67±291.71

0 - 2 months : $p < 0.05$

Table XVII shows the effect of Lisinopril on 24 hours urinary albumin excretion in patients on insulin. Initially 24 hours protein excretion was 351.87±304.43 mg/24 hours while it was found to be 220.67±291.71 mg/24 hours at 2 months and the difference was significant statistically ($p < 0.05$).

TABLE XVIII : Showing the statistical comparison of table XVI and XVII.

Treatment group (Insulin)	Values of albuminuria (Mean±S.D.)	
	0 month	2 months
Enalapril	245.23±256.79	216.30±219.53
Lisinopril	351.87±304.43	220.67±291.71
p value	>0.05	>0.05

Table XVIII shows the comparison of 0 and 2 months of table XVI and XVII. At both times the difference in values of urinary protein excretion was statistically insignificant (p >0.05).

TABLE XIX : Showing the effect of Enalapril on blood urea in patients on oral hypoglycemic agents.

Case No.	Blood urea (mg/dl)	
	0 month	2 months
1	30	26
2	20	22
3	63	50
4	25	26
5	24	28
6	24	25
7	23	26
8	36	38
9	65	60
10	23	20
11	50	54
12	40	46
Mean±S.D.	35.08±15.66	35.00±13.97

0 - 2 months : p >0.05

Table XIX shows the effect of Enalapril on blood urea in patients on oral hypoglycemic agents. Initially the blood urea level was 35.08±15.66 mg/dl and it fell to 35.00±13.97 mg/dl after 2 months therapy and the difference was statistically insignificant (p 70.05).

TABLE XX : Showing the effect on Lisinopril on blood urea in patients on oral hypoglycemic agents.

Case No.	Blood urea (mg/dl)	
	0 month	2 months
1	40	46
2	30	36
3	56	52
4	46	44
5	24	20
6	28	30
7	40	38
8	40	42
9	36	38
10	26	30
11	33	20
12	34	20
13	25	26
14	20	22
15	24	20
16	60	46
Mean±S.D.	34.50±11.85	33.75±10.50

0 - 2 months : p 70.05

Table XX shows the effect of Lisinopril on blood urea in patients on oral hypoglycemic agents. Initially the blood urea was 34.50±11.85 mg/dl which came down to 33.75±10.50 mg/dl after 2 months therapy and difference between values at 0 month and 2 months was statistically insignificant (p 70.05).

TABLE XXI : Showing statistical comparison of tables XIX and XX.

Treatment group (oral hypoglycemic agents)	Blood urea(mg/dl) (mean±S.D.)	
	0 month	2 months
Enalapril	35.08±15.66	35.00±13.97
Lisinopril	34.50±11.85	33.75±10.50
p values	70.05	70.05

Table XXI shows the statistical comparison of tables XIX and XX at 0 month and 2 months and it was found that there was no statistical difference between the values at 0 and 2 months (p 70.05).

TABLE XXII : Showing the effect of Enalapril on blood urea in patients on insulin.

Case No.	Blood urea (mg/dl)	
	0 month	2 months
1	38	40
2	34	32
3	36	35
4	30	32
5	24	22
6	45	43
7	26	30
8	40	38
9	32	34
10	33	31
11	28	30
12	38	36
13	46	44
Mean±S.D.	34.62±6.79	34.38±5.98

0 - 2 months : $p > 0.05$

Table XXII shows the effect of Enalapril on blood urea in patients on insulin. It was 34.62±6.79 mg/dl at 0 months and it decreased to 34.48±5.98 mg/dl after 2 months of therapy but the difference was not statistically significant ($p > 0.05$).

TABLE XXIII : Showing the ffect of Lisinopril on blood urea in patients on insulin.

Case No.	Blood urea (mg/dl)	
	0 month	2 months
1	38	34
2	28	26
3	42	40
4	35	30
5	30	36
6	40	38
7	46	48
8	24	20
9	40	30
10	48	44
11	36	42
12	24	30
13	30	34
14	42	40
15	24	28
Mean±S.D.	35.13±8.06	34.63±7.64

0 - 2 months : p /0.05

Table XXIII shows the effect of Lisinopril on blood urea in patients on insulin. It was 35.13±8.06 mg/dl at 0 months and it decreased to 34.63±7.64 mg/dl at 2 months of the therapy but the difference was not statistically significant (p /0.05).

TABLE XXIV : Showing the statistical comparison of tablesXXII and XXIII.

Treatment group (Insulin)	Blood urea (Mean±S.D., mg/dl)	
	0 month	2 months
Enalapril	34.62±6.79	34.38±5.98
Lisinopril	35.13±8.06	34.63±7.64
p value	>0.05	>0.05

Table XXIV shows the statistical comparison of tables XXII and XXIII at 0 and 2 months and it was found that there was no statistical significant difference between the values at 0 and 2 months(p >0.05).

TABLE XXV : Effect of Enalapril on serum creatinine in patients on oral hypoglycemic agents.

Case No.	Serum creatinine (mg/dl)	
	0 months	2 months
1	0.9	1.3
2	1.0	1.0
3	1.3	1.1
4	0.9	1.2
5	1.3	1.2
6	1.0	1.5
7	1.3	1.1
8	1.2	1.1
9	1.5	1.4
10	1.2	1.1
11	1.4	1.5
12	1.8	1.6
Mean±S.D.	1.23±0.26	1.25±0.20

>0.05

Table XXV shows the effect of Enalapril on serum creatinine in patients on oral hypoglycemic agents. Initially it was 1.23±0.26 mg/dl and it increased to 1.25±0.20 mg/dl after 2 months of therapy. The difference was not significant statistically (p >0.05).

TABLE XXVI : Showing the effect of Lisinopril on serum creatinine in patients on oral hypoglycemic agents.

Case No.	Serum creatinine (mg/dl)	
	0 month	2 months
1	1.8	2.1
2	1.2	1.3
3	2.0	1.9
4	1.3	1.7
5	1.0	1.1
6	1.2	1.0
7	1.1	0.9
8	0.8	1.0
9	1.6	1.9
10	1.0	1.1
11	0.9	0.8
12	1.1	1.0
13	1.2	1.1
14	0.9	0.8
15	1.0	1.1
16	1.5	1.4
Mean±S.D.	1.23±0.33	1.26±0.41

0 - 2 months : p >0.05

Table XXVI shows the effect of Lisinopril on serum creatinine in patients on oral hypoglycemic agents. The mean value at 0 month was 1.23±0.33 mg/dl and it was slightly increased to 1.26±0.41 mg/dl after 2 months of treatment but it was insignificant statistically (p >0.05).

TAVLE XXVII : Statistical comparison between tables XXV and XXVI.

Treatment group (Oral hypoglycemic agents)	Serum creatinine (Mean±S.D., mg/dl)	
	0 month	2 months
Enalapril	1.23±0.26	1.25±0.20
Lisinopril	1.26±0.33	1.26±0.41
p values	>0.05	>0.05

Table XXVII shows the comparison of tables XXV and XXVI. It was found that at 0 and 2 months there was no statistical difference between the values of two treatment groups (p >0.05).

TABLE XXVIII : Showing the effect of Enalapril on serum creatinine in patients on insulin.

Case No.	Serum creatinine (mg/dl) 0 month	2 months
1	1.6	1.4
2	1.3	1.2
3	1.8	1.6
4	1.4	1.3
5	1.3	1.4
6	1.4	1.2
7	1.5	1.4
8	1.0	1.4
9	1.2	1.5
10	1.3	1.2
11	1.4	1.3
12	1.3	1.2
13	1.5	1.4
Mean±S.D.	1.38±0.20	1.35±0.13

0 - 2 months : p $>$ 0.05

Table XXVIII shows the effect of Enalapril on serum creatinine in patients on insulin. The mean values of 1.38±0.20 mg/dl fell down to 1.35±0.13 mg/dl after 2 months therapy. But the difference was not statistically significant (p $>$ 0.05).

TABLE XXIX : Showing the effect of Lisinopril on serum creatinine in patients on insulin.

Case No.	Serum creatinine (mg/dl)	
	0 month	2 months
1	1.8	1.6
2	1.6	1.6
3	2.0	1.8
4	1.3	1.6
5	1.1	1.5
6	1.7	1.6
7	2.4	1.8
8	1.0	1.1
9	1.1	1.0
10	1.8	1.7
11	1.2	1.3
12	1.1	1.0
13	1.2	1.0
14	1.7	1.3
15	1.3	1.4
Mean±S.D.	1.49±0.41	1.42±0.29

0 - 2 months : $p > 0.05$

Table XXIX shows the effect of Lisinopril on serum creatinine in patients on insulin. Initially it was 1.49±0.41 mg/dl and it came down to 1.42±0.29 mg/dl after 2 months of therapy. The difference was not significant statistically ($p > 0.05$).

TABLE XXX : Showing statistical comparison between tables XXVIII and XXIX.

Treatment group (Insulin)	Serum creatinine (Mean±S.D., mg/dl)	
	0 month	2 months
Enalapril	1.38±0.20	1.35±0.13
Lisinopril	1.49±0.41	1.42±0.29
p values	>0.05	>0.05

Table XXX shows the statistical comparison between tables XXVIII and XXIX at 0 and 2 months interval and it was found that there was no statistical difference between the values at 0 and 2 months.

D I S C U S S I O N

D I S C U S S I O N

Present study was carried out in 56 patients of diabetic nephropathy, who were attending diabetic clinic regularly at M.L.B. Medical College, Hospital, Jhansi. Out of 56 patients, 25 patients were included in Enalapril group and remaining 31 patients in Lisinopril group.

ENALAPRIL GROUP

Twenty five patients were included in Enalapril group, 17 were males and 8 were females. Maximum number (40%) of cases belonged to age group 41-50 years. Out of 25 patients, 12 (40%) patients were on oral hypoglycemic agents and rest 13 (52%) were on insulin therapy.

LISINOPRIL GROUP

Thirty one cases were included in Lisinopril group. Out of which, 20 were males and 11 were females. Maximum number (64.58%) of cases belonged to 50-70 years of age group. Out of 31 patients, 16(51.60%) patients were on oral hypoglycemic agents and rest 15 were on insulin therapy.

Maximum duration of diabetes mellitus in Enalapril group was 6-10 years in 15(60%) patients, while in Lisinopril group the maximum duration was 11-15 years in 12(38.71%) patients.

Bjorck Staffan et al (1985) studied the 15 patients of diabetic nephropathy who were insulin dependent and mean duration of diabetes mellitus was 22 years. While in present study short duration of diabetes mellitus could be because of late diagnosis due to illiteracy and poor status, patients report very late to the physician/ hospital.

EFFECT OF BLOOD PRESSURE

Enalapril Group

In oral hypoglycemic group , mean systolic blood pressure at 0 month was 136.0±17.75 mm Hg which came down to 132.0±20.45 mm Hg after 2 months. This change was statistically significant ($p < 0.05$). Similarly the diastolic blood pressure fell from initial 85.0±7.70 mm Hg to 82.33±8.55 mm Hg after two months. This decrease was also significant statistically ($p < 0.05$).

Similarly, significant fall ($p < 0.05$) in both systolic blood pressure (134.46±19.02 to 131.38±15.95 mm Hg) and diastolic blood pressure (82.0±10.65 to 80.46± 9.32 mm Hg) was observed in patients on insulin therapy who were given Enalapril.

Ueda, Aoi, Yamachika et al (1990) showed that Enalapril therapy significantly produce a fall in blood pressure, increase the blood flow, produces a change in GFR.

According to Mogensen et al (1991) also ACE inhibitors are effective on systemic hypertension.

Ciavarella and Mutachio et al (1992) observed that administration of Enalapril (5-10 mg/day) in normotensive and hypertensive type I (insulin depedent) diabetic patients resulted in a significant fall in mean arterial pressure.

LISINOPRIL GROUP

In oral hypoglycemic group the mean systolic blood pressure fell from 152.13±27.99 to 140.38±23.22 mm Hg. This change was significant statistically ($p < 0.05$), while mean diastolic blood pressure fell from initial 88.88±15.42 to 85.38±8.88 mm Hg after 2 months therapy and this decrease was also significant statistically ($p < 0.05$).

Similarly in insulin group, the mean systolic blood pressure fell from 147.47±20.97 to 139.73±19.34 mm Hg and this change was significant statistically ($p < 0.05$), while mean diastolic blood pressure fell from 85.07±10.74 mm Hg to 82.27±8.65 mm Hg and this change was also significant ($p < 0.05$). In this group 47% patients were having hypertension.

Barkis et al (1994) observed a significant fall in mean arterial pressure after 18 months treatment with Lisinopril in normotensive, insulin dependent diabetic (IDDM) patients.

EFFECT ON PROTEINURIA

In Enalapril group, 24 hours urinary albumin excretion in patients on oral hypoglycemic agents fell

down from initial 202.33±249.84 to 180.83±266.80 mg and this fall was statistically insignificant (p >0.05), while in insulin group mean urinary albumin excretion came down from initial 245.33±256.79 mg/24 hours to 216.30±219.53 mg/24 hours and this difference was also statistically insignificant.

In Lisinopril group, mean urinary albumin excretion in patients on oral hypoglycemic agents fell down from initial 340.00±298.70 mg/24 hours to 278.75 ±286.25 mg/24 hours and this difference was statistically insignificant (p >0.05), whereas in insulin group initial mean albumin excretion was 351.87±304.43 mg/24 hours and fell to 220.67±291.71 mg/24 hours after two months therapy and this difference was statistically significant (p <0.05).

Bauer and Reams (1992) observed that Enalapril therapy was associated with significant initial (46%) and sustained (33%) decrease in proteinuria in their 18 months trial on clinical diabetic nephropathy. They also reported that clinical course of renal disease in type I and type II diabetic patients randomised to Enalapril therapy did not differ.

Barkis et al (1992) , Stornello et al (1992), Ferder et al (1992), Ravid et al (1993) and O'Donnel et al, (1993) also showed that ACE inhibitors reduce the proteinuria in type II diabetic patients with nephropathy.

In other studies viz. Heeg et al (1989), Bjorck (1992), Marre (1987), Rudberg (1990), Slomowitz (1990),

Alfred Aperloo et al (1991) and Stataper (1993), Christeinsen et al (1988) also showed ACE inhibitors have an antiproteinuric potential in type I diabetic patients with nephropathy.

In this study both Enalapril and Lisinopril were associated with decrease in 24 hour urinary albumin but this decrease was not significant ($p > 0.05$). In patients on insulin in Lisinopril group, the fall in urine albumin was significant and it may be due to better metabolic control by insulin than oral hypoglycemic agents.

EFFECT ON RENAL FUNCTIONS

Blood Urea

In present study 12 patients on oral hypoglycemic group treated with Enalapril and 16 patients with Lisinopril. In Enalapril group initially the mean blood urea was 35.08 ± 15.66 mg/dl which fell down to 35.0 ± 13.97 mg/dl after 2 months treatment. This difference was statistically insignificant ($p > 0.05$). In Lisinopril group, the mean value of blood urea, came down from initial 34.50 ± 11.85 mg/dl to 33.75 ± 10.50 mg/dl and again this difference was insignificant ($p > 0.05$).

Similarly in insulin group, 13 patients were treated with Enalapril and 15 patients with Lisinopril. In Enalapril group mean blood urea fell down from initial values of 34.62 ± 6.79 mg/dl to 34.48 ± 5.98 mg/dl after two months therapy and this difference was statistically insignificant ($p > 0.05$). Similarly in Lisinopril group mean blood urea came down from initial mean value of

35.13±8.06 to 34.63±7.64 mg/dl and it was also insignificant statistically ($p > 0.05$).

Statistically comparison of both drugs shows that effects of Enalapril and Lisinopril are same ($p > 0.05$) on blood urea.

SERUM CREATININE

Same patients were also investigated for serum creatinine before and after 2 months of therapy. In oral hypoglycemic group, patients on Enalapril therapy, the mean serum creatinine increased from 1.23±0.26 to 1.25± 0.20 mg/dl but in patients on Lisinopril therapy the values were almost same (1.26±0.33 and 1.26±0.41 mg/dl) before and after 2 months of therapy. The changes were not statistically significant ($p > 0.05$).

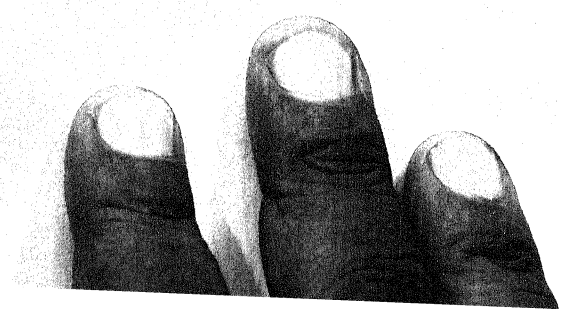
Similarly in insulin group, patients on Enalapril therapy serum creatinine decreased from 1.38±0.20 to 1.35± 0.13 mg/dl but in patients on Lisinopril therapy, the mean value decreased from 1.49±0.41 to 1.41±0.29 mg/dl. These changes were statistically insignificant ($p > 0.05$).

Statistical comparison of both drugs shows that effects of Enalapril and Lisinopril are the same ($p > 0.05$) on serum creatinine.

On comparing, results showed that effect of Enalapril and Lisinopril on renal function are almost same and it was maintained throughout the study period.

According to Taguma et al (1985), Mogensen et al (1982), Bjorck et al (1986), Hammel et al (1986) Marre et al (1987), Parving et al (1988) the effect of angiotensin converting enzyme inhibitors on renal function was almost same and maintained through out the study period.

C O N C L U S I O N



B I B L I O G R A P H Y

C O N C L U S I O N

In this study, 25 patients in Enalapril group and 31 patients in Lisinopril group were studied to find out the effect on albuminuria and renal function in hypertensive and normotensive patients of diabetic nephropathy. The comparative effect of both drugs was also analysed.

The following conclusions were drawn from the present study :

1. The effect of both Lisinopril and Enalapril is equally good in reducing blood pressure in hypertensive diabetic patients. The fall in blood pressure was statistically significant ($p < 0.05$) in both Enalapril and Lisinopril group.
2. The albuminuria in both Lisinopril and Enalapril group after 2 months of treatment decreased but it was statistically insignificant ($p > 0.05$) except in insulin treated diabetics with Lisinopril in which fall is significant ($p < 0.05$).
3. Statistical insignificant changes were observed on blood urea and serum creatinine in both groups.
4. Overall results shows that Enalapril and Lisinopril have almost same effect on hypertension, albuminuria and renal function in diabetic nephropathy.

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